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CASE REPORT

The 'sweet killer'

Can you recognize the symptoms of ethylene glycol poisoning?

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Each year, about 6,000 Americans are poisoned by ethylene glycol, a main ingredient in automotive antifreeze. Early diagnosis and aggressive treatment are essential to prevent permanent disability or death. The authors describe a case of severe ethylene glycol intoxication in which fast action prevented serious long-term complications.
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An 84-year-old woman weighing 121 lb (55 kg) with no previous history of alcoholism was stuporous on presentation at the emergency department. Her family had found her obtunded and reported that she had complained earlier of blurred vision and had had one episode of emesis.

On physical examination, blood pressure was 107/54 mm Hg, pulse rate 60 beats per minute, and respirations 16 per minute. The lungs were clear and heart rate was regular, with occasional premature beats. Funduscopic examination was unremarkable, and neurologic examination showed no evidence of focal deficits. The remainder of the examination was unremarkable.

A computed tomographic scan of the head and a lumbar puncture were normal. Results of laboratory testing were the following: serum sodium 146 mEq/L, potassium 4.2 mEq/L, chloride 107 mEq/L, bicarbonate 14 mEq/L, serum urea nitrogen 10 mg/dL, creatinine 1.4 mg/dL, blood glucose 148 mg/dL, total serum calcium 10 mg/dL, phosphorus 5.1 mg/dL, magnesium 2.8 mg/dL, lactate 2.1 mg/dL. A ketone screening test was negative, liver function tests were within normal limits, and serum ethanol was less than 10 mg/dL. An initial urinalysis was normal, but a second sample contained calcium oxalate crystals. Arterial blood gas analysis values were pH 7.12, PaO2 71 mm Hg, and PCO2 30 mm Hg. Calculated osmolality was 307.7 mOsm/kg of water and serum osmolality was 354 mOsm/kg of water, resulting in an osmolal gap of 46.2.

A working diagnosis of metha-nol intoxication (based on possible blurred vision) or, more likely, ethylene glycol intoxication (based on the second urinalysis) was made. The family reported that the patient's poor eyesight may have led her to mistakenly ingest some antifreeze, which had been diluted with water in a 2-L plastic soda bottle and left in the kitchen. Ethylene glycol intoxication was confirmed when the patient's drinking cup was brought in for examination and found to contain remnants of

antifreeze.

Gastric lavage was immediately performed, followed by administration of oral activated charcoal as well as 5% dextrose in normal saline solution, 75 mL/hr, and 2 ampules of sodium bicarbonate, given intravenously. The patient was intubated for airway protection and an intravenous loading dose of 10% ethanol was given, followed by a maintenance dose of 77 mL/hr (127 mg/hr). Intravenous thiamine hydrochloride and pyridoxine hydrochloride were also given, and hemodialysis was performed when serum ethylene glycol reached 217 mg/dL.

After 10 days, the patient was discharged on her baseline health status. Follow-up continued in our outpatient clinic, but she had no lasting sequelae. We believe early intervention and rapid treatment contributed to a full recovery from severe intoxication.

Discussion

Ethylene glycol, sometimes referred to as the "sweet killer," is an odorless, colorless, water-soluble liquid that is used as a main ingredient in automotive antifreeze and other products (1). Most ethylene glycol poisonings result from suicide attempts, accidental ingestion, or improper substitution for alcohol owing to its inebriating effects (2,3).

Intoxication is actually caused by the acidic metabolites of ethylene glycol, which explains the latent period of the toxic syndrome (1,2,4,5). Ethylene glycol has such a high molecular weight that even toxic amounts may contribute only modestly to a patient's overall serum osmolality, compared with related alcohols at a lethal level (table 1) (4).

Table 1. Properties of ethylene glycol and related alcohols that affect serum osmolality

Alcohol	Molecular weight (D)	Lethal level (mg/dL)	Corresponding change in osmolality
Ethylene glycol	62	21	3.4-4
Methanol	32	80	25
Isopropanol	60	340	56
Ethanol	46	350	76

D, daltons

Ingested ethylene glycol is readily absorbed and reaches peak serum levels in 1 to 4 hours. The volume of distribution is 0.6 L/kg of body weight and the half-life is 3 hours. Ethylene glycol is metabolized by the liver enzyme alcohol dehydrogenase into four toxic metabolites: glycoaldehyde, glycolic acid, glyoxylic acid, and oxalic acid (figure 1: not shown) (2,5,6). These metabolites can cause central nervous system (CNS) depression, cardiopulmonary failure, and renal failure (1-8).

Diagnosis is based on history taking, clinical presentation, and three key laboratory findings: high- anion-gap metabolic acidosis, high osmolality with osmolal gap, and oxalate crystalluria (1,9).

Clinical and laboratory findings may be typical for the diagnosis, but the presence of ethylene glycol depends on the interval between ingestion and evaluation. Thorough history taking from the patient, family, or friends is always essential to a rapid diagnosis. Unfortunately, historical details may be unavailable because of CNS depression or the circumstances of the intoxication.

Clinical manifestations are thought to evolve in three stages, depending on the latency of the intoxication and the amount of ethylene glycol ingested (1,3). However, these stages may not be clearly defined or may overlap.

CNS manifestations, such as somnolence, disorientation, agitation, inebriation, and confusion, occur 30 minutes to 12 hours after ingestion. Deeper CNS depression, such as stupor or coma, may occur in 12 to 24 hours (1). Associated laboratory abnormalities may include high-anion-gap metabolic acidosis, high osmolal gap, hyperkalemia, hypocalcemia, and oxalate crystalluria (1).

Cardiopulmonary manifestations (eg, heart failure, noncardiac pulmonary edema) occur 12 to 24 hours after ingestion. Signs and symptoms include hypertension, tachycardia, dyspnea, tachypnea, and Kussmaul's respirations caused by metabolic acidosis (1).

Renal failure occurs 24 to 72 hours after ingestion. In patients who survive intoxication, renal failure secondary to acute tubular necrosis may present with proteinuria, oliguria, and anuria. Renal failure may be permanent, but it typically is acute and resolves within days or a few weeks. It is thought that renal edema and oxalate crystal precipitation cause decreased renal blood flow, thereby contributing to acute renal failure.

The laboratory findings are striking. It is thought that metabolic acidosis associated with ethylene glycol intoxication is due primarily to the presence of glycolic acid and, to a lesser extent, other organic acids (eg, lactic acid) (1,2,5). Oxalate also appears to precipitate as calcium oxalate in different organs (eg, brain, heart, kidneys, lungs, pancreas) and in the urine, leading to the hypocalcemia that is typical of ethylene glycol poisoning (1,2).

A low anion gap is usually caused by decreased albumin, while an increased anion gap is most commonly caused by metabolic acidosis in which bicarbonate is titrated to organic acids (10). An anion gap greater than 25 is almost always secondary to the presence of an organic acid and is typical of ethylene glycol intoxication. The metabolites glycolic acid and lactate that cause increased-anion-gap metabolic acidosis may be absent in patients who present very soon after ethylene glycol ingestion.

The precipitation of calcium oxalate in the renal tubules results in the oxalate crystalluria that is present on admission in 50% of patients (2). Because oxalate is a by-product of ethylene glycol metabolism, it may not be evident early in the presentation, as was the case in our patient. It is also thought that calcium oxalate precipitation in other organs may partially explain the organ damage as well as hypocalcemia (2).

The osmolal gap can be helpful in diagnosing ethylene glycol intoxication because ethylene glycol increases serum osmolality and the osmolal gap before it is completely metabolized. The osmolal gap is usually measured using vapor pressure osmometry or the freezing point method. Because ethylene glycol is a volatile chemical, only the latter method is reliable when considering possible intoxication. Typically, an osmolal gap greater than 10 mOsm/kg of water is considered abnormal (1,7), but it has been recommended that levels greater than 15 or even greater than 20 mOsm/kg of water be used as a reference for the presence of unmeasured solutes (2). This controversy is based on the pitfalls involved in considering the osmolal gap, which include the previously mentioned methods of measuring serum osmolality, the high molecular weight of ethylene glycol, the variety of formulas for the calculation of osmolality, and the fact that only unmetabolized ethylene glycol contributes to increased osmolality (2,4). Although increased osmolality may be helpful in diagnosing ethylene glycol poisoning, it is an unreliable screening tool (4).

Fluorescein is usually added to antifreeze to color it and thereby help detect radiator leaks. The presence of fluorescein also may be helpful in diagnosis of ethylene glycol intoxication, and it may be detected in the stomach contents, urine, or skin using Wood's light (3).

A differential diagnosis should be considered with all the signs and symptoms (ie, CNS depression, overdose, substance abuse) at presentation. CNS depression is suggestive of cerebrovascular accident, CNS infection, drug use, or metabolic disturbances. Often, the presentation narrows the diagnosis to increased-anion-gap metabolic acidosis, which is usually caused by certain drug therapies (ie, aspirin, ferrous sulfate, isoniazid [Laniazid, Nydrazid], paraldehyde [Paral]), alcoholic metabolic ketoacidosis, diabetic ketoacidosis, uremia, lactic acidosis, methanol, or ethanol (1). An increased osmolal gap may be caused by ethyl alcohol, ethylene glycol, methanol, isopropanol, or mannitol. The presence of calcium oxalate in the urine is suggestive of ethylene glycol intoxication and can be confirmed with appropriate laboratory tests.

Successful therapy requires early diagnosis and treatment with ethanol and hemodialysis; vitamin cofactors may be used (2). It is important to ensure standard initial stabilization and adequate airway protection and to maintain vital signs and urine output. Gastrointestinal decontamination using gastric aspiration followed by lavage is beneficial if performed within 1 to 2 hours of ingestion. Ipecac is contraindicated owing to CNS depression. Activated charcoal (Actidose-Aqua, CharcoAid 2000, Liqui-Char) is not useful for

ethylene glycol poisoning, but it may be used in the presence of a coingestant (2). If hypocalcemia-induced seizure occurs, intravenous calcium therapy should be considered. However, this therapy should be given only for symptomatic hypocalcemia because of the possibility of calcium oxalate precipitation.

Metabolic acidosis should be aggressively treated until the serum bicarbonate level is at least 10 mEq/L; at least 500 to 1,000 mEq/L of sodium bicarbonate may be required (2). Complications of this therapy include hypernatremia, fluid overload, and worsening hypocalcemia.

More specific treatment using antidotal agents, such as ethanol and fomepizole (Antizole), inhibits alcohol dehydrogenase and prevents the metabolism of ethylene glycol to its toxic by-products (8). Ethanol has been the primary specific antidotal therapy for ethylene glycol poisoning. Alcohol dehydrogenase has 100 times greater affinity for ethanol than for ethylene glycol. Ethanol increases ethylene glycol's half-life from 3 to 17 hours, thus allowing the latter to be excreted unchanged in the urine (3). Ethanol should be administered intravenously or nasogastrically as a loading dose of 0.6 g/kg of body weight, followed by an intravenous maintenance dose of 66 to 154 mg/kg of body weight per hour using a 5% to 10% solution (2,3). The goal is to reach a serum ethanol level of 100 to 200 mg/dL and continue the infusion until ethylene glycol levels are undetectable. Ethanol levels should be checked often because ethanol metabolism varies greatly. The maintenance rate for ethanol infusion should be increased to 237 mg/kg of body weight per hour for patients undergoing hemodialysis (1). Indications for ethanol therapy include a strong suspicion of ethylene glycol ingestion, a serum ethylene glycol level of 20 mg/dL or greater, and presence of significant metabolic acidosis, regardless of ethylene glycol level. Adverse effects of ethanol therapy include gastric or vein irritation (depending on the route of administration), CNS depression, and hypoglycemia.

Fomepizole, also known as 4-methylpyrazole, is a newer antidote for ethylene glycol intoxication. Like ethanol, it inhibits alcohol dehydrogenase, but it is more potent and has fewer potential adverse effects. Although this agent was not available in the United States at the time of our patient's presentation, studies (10-12) have since shown it to be of benefit.

The use of hemodialysis for ethylene glycol intoxication is controversial, but generally it is used in the presence of refractory acidosis or difficulty in management with sodium bicarbonate and ethanol, unstable vital signs, progressive deterioration, ethylene glycol levels greater than 50 mg/dL, or renal failure. Hemodialysis should continue until ethylene glycol levels fall below 10 mg/dL, metabolic acidosis is corrected, adequate urine output is achieved, and the patient's condition is stabilized.

Thiamine hydrochloride (Biamine) and pyridoxine hydrochloride (Beesix) have also been used in the treatment of ethylene glycol poisoning. These cofactors theoretically promote the formation of less toxic metabolites of ethylene glycol (figure 1: not shown) (1,2). The recommended dose of thiamine is 100 mg, given intramuscularly or intrave-nously every 6 hours. Pincus and colleagues (1) recommend doses of 50 to 500 mg of pyridoxine, given intravenously or intramuscularly every 6 hours. However, the use of pyridoxine is controversial because of insufficient data and the risk of peripheral neuropathy. If pyridoxine is used, we recommend that it be given at the lower dose.

Summary

Ingested ethylene glycol is readily absorbed and metabolized into toxic metabolites that can cause CNS depression, cardiopulmonary failure, and renal failure. Thorough history taking, physical examination, and laboratory testing are essential for diagnosis. Careful differential diagnosis is important because symptoms of ethylene glycol poisoning are similar to those of other intoxicants. Early, aggressive treatment with appropriate therapies, such as ethanol therapy, hemodialysis, vitamin cofactors, and antidotal agents, is necessary to prevent permanent disability or death.

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Calculating anion gap and osmolal gap

Anion gap

$AG = [Na^+] - ([Cl^-] + [HCO_3^-])$

Normal anion gap = 8-12

Osmolal gap

OG = calculated osmolality - measured osmolality, where

$$\text{calculated osmolality} = 2[Na^+] + \frac{\text{blood glucose}}{18} + \frac{\text{serum urea nitrogen}}{2.8}$$

To this formula add $\frac{\text{ethanol (g/dL)}}{4.6}$ to correct the contribution of ethanol to the measured osmolality

AG, anion gap; OG, osmolal gap.

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RETURN TO OCTOBER 1, 1999 TABLE OF CONTENTS

about us | cme | home | issue index | patient notes | pearls | ad services |